

# Molecular diagnosis of neurogenetic diseases of children in China: the current status and the future

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With the development of socioeconomy and science and technology, the morbidity and mortality of infectious diseases have dramatically decreased, and the spectrum of pediatric diseases has changed a lot. Inferred from the regular developmental pattern of the world, when the infant mortality of a country decreased to the level below 40‰, birth defects and genetic diseases will become a big problem. In 2004, the infant mortality of the rural and urban areas is 24.6‰ and 10.1‰ respectively in China.<sup>[1]</sup> The new concept raised by WHO suggests that any kind of human disease is related to or consists of genetic elements. Genetic diseases are becoming a big problem in public health in China.<sup>[2]</sup>

According to the statistical data from OMIM (Online Mendelian Inheritance in Man), most of the 17 294 (December 13, 2006) human genetic diseases are implicated with the nervous system, and often flare up in childhood. The Center for Disease Control of America reported that about 25% to 39% of patients in pediatric hospitals suffered from genetic diseases. Taking the Neurological Division of Pediatric Department at Peking University First Hospital as an example, 26.2% of the inpatients in 2004 were diagnosed as having neurogenetic diseases, excluding genetic epilepsy.<sup>[3]</sup>

Children's neurogenetic diseases with complicated clinical symptoms and high heterogeneities are difficult to diagnose correctly and timely. The high deformity and mortality or the resultant mental and motor developmental problems of children with this disease often put a heavy psychological and economical burden on the family and society since there has been no

effective treatment. Diagnosis of neurogenetic diseases in children depends on clinical manifestations, family history, neurophysiology, biochemistry, immunology, imaging, pathology, etc. In the past few years, meetings, training courses and books have contributed to the clinical diagnosis and treatment of the diseases as well as the research. Additional advanced technologies such as neuroimaging including CT and MRI, neuropathology (skin, nerve and muscle biopsy), neurophysiological and biochemical examinations (GC-MS, MS-MS, enzyme examination) have ensured timely diagnosis of many diseases including disorders of organic acid and amino acid metabolism, mitochondrial encephalomyopathy, inherited leukoencephalopathy, etc. Thus the definite diagnosis has further driven such effective treatments as biotin for multiple carboxylase deficiency, carnitine for organic aciduria, and mitochondrial encephalomyopathy and many other dietary prescriptions. A small number of the diseases such as X-linked adrenoleukodystrophy are diagnosed by the elevated level of very long chain fatty acid (VLCFA) in blood<sup>[4]</sup> and then prenatal diagnosis for the disease can be initiated. Clinical centers for inborn errors of metabolism in different hospitals in China play an important part in clinical diagnosis and treatment of the diseases and in professional exchanges worldwide.

Despite of the great progress in clinical diagnosis and treatment, many neurogenetic diseases of children are still not diagnosed correctly. Among the undoubted ones, their pathogenesis is still vague. Presently, a series of difficulties remain in clinical diagnosis and treatment of a disease with different phenotypes. It is difficult to find reliable markers for prenatal and pre-symptomatic diagnosis, targeted treatment or intervention. Thus population-based investigation and public prevention are impossible because of lack of certain markers for the diagnosis of the illness, making detecting carriers difficult. However, accomplishment of human genome projects and the development of molecular genetic technology have made the analysis of known disease genes of patients possible. Clinical diagnosis of neurogenetic diseases in children has evolved from

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phenotypic and chemical to molecular level. In the past decade, lots of disease genes have been confirmed in the field of neuroscience, such as KCNQ2/KCNQ3 for benign familial neonatal convulsion and MECP2 for Rett syndrome. "Clinical molecular diagnosis" is different from "clinical molecular research". Molecular diagnosis is not merely an isolated analysis of a family, but should be based on molecular research through a series of clinical verifications to confirm types of gene mutation, mutation frequency, regular distribution patterns of diseases in different ethnic populations. Molecular diagnosis is advantageous in the "confirmation" of diseases, and in facilitating pathogenic research and prenatal and pre-symptomatic diagnosis. The confirmation of disease genes and the mechanism of diseases may lead to the production of effective drugs for the prevention and treatment.

The so-called "gene diagnosis" in most hospitals or institutes in China is still at the stage of clinical molecular research. To establish a standard clinical gene diagnosis in the future, it is necessary to standardize the diagnostic procedures, carry out clinical molecular research properly, and collect data rationally.

The recently published articles on the clinical molecular diagnosis of neurogenetic diseases in children in China cover infantile neuronal ceroid lipofuscinoses, benign familial neonatal convulsion, and dopa-responsive dystonia. Others include studies of Duchenne muscular dystrophy,<sup>[5]</sup> spinal muscular atrophy,<sup>[6]</sup> childhood absence epilepsy,<sup>[7]</sup> Rett syndrome,<sup>[8]</sup> X-linked adrenoleukodystrophy and Leigh disease,<sup>[9]</sup> correlation between genotype and phenotype, and gene functional study.<sup>[10,11]</sup> In short, the increased diagnostic level of neurogenetic diseases in Chinese children is characterized by much work on exploration of the types and features of mutation of known genes; little work on new susceptibility genes and investigation of their function; much attention to genetic resources such as registration, collection and follow-up of the family diseases; emphasizing the relationship between genotype and phenotype; and the cooperation between clinical and genetic studies.

With a good beginning in clinical research of children's neurogenetic diseases at the molecular level, we should pay more attention to its reliability and credibility. DNA sequencing results are usually taken as the diagnostic basis, but before using it in clinical diagnosis, the results of DNA sequencing must be analyzed by the secondary approaches such as RFLP analysis and southern blot. For the molecular examinations which have been tested and validated several times in clinical practice, they can be transferred from the research laboratory to the clinical laboratory. Only at this time, can we report the result to

the parents of children.

Standardized clinical gene diagnosis is dependent on the data of a large number of cases collected from a series of molecular research. Thus disease gene's characteristics can be summarized. After a series of clinical evaluation, the proved gene analysis method can be used to determine certain mutation of the causative gene. At this time the so-called "clinical gene diagnosis" becomes a reality.

In China, molecular analysis is still in the period of exploration and research, and needs to be proved and validated by geneticists and other related organizations. In clinical practice, pediatricians and pediatric neurologists should pay attention to the following points:

1. Patients and their parents should be informed the fact that the molecular analysis in China is still in the initial stage of research. In North America, the results of molecular examination are not reported to the patients or their relatives. But informed consent is needed before this kind of examination is done in addition to the protection of the privacy and confidentiality of patients.

2. Molecular analysis is clearly defined to increase the diagnostic rate of neurogenetic diseases and clarify genotypes and phenotypes of certain diseases, providing a foundation for pre-symptomatic and prenatal diagnosis and treatment. So pediatricians should first determine correctly clinical phenotypes by all kinds of technologies, and try their best to map the pedigree of certain diseases.

3. The significance of the results of molecular analysis should be evaluated with the help of geneticists. As soon as a new DNA sequence alteration is found, it is imperative to confirm whether it is a mutation or a polymorphism. After confirmation, multidisciplinary cooperation is required to study the function of causative genes and their mechanisms, which will guide future treatment.

4. In genetic counseling, pediatricians must provide information about inheritance pattern, clinical manifestations, sibling disease risk, and treatment regimen. The data or files of diseases of each family member should be kept and easily traced.

Data collection, registration and processing are important. Cooperation between clinical fields is emphasized to share the resources and to make the results of large-sample studies reliable. Additionally, pediatricians should learn from medical genetic specialists.

In the USA, Europe and Hong Kong, medical genetics has become an important linkage between basic and clinical medicine. Clinical diagnosis, treatment, and counseling of genetic diseases have

become legal issues and a major component of public health promotion.

In America, among 1335 kinds of strictly validated genetic examinations, 1034 have been used in clinical diagnosis, most of which are directed against single gene disease.<sup>[12,13]</sup> In Hong Kong, the medical institutes provided genetic counseling for 20 965 families from 1981 to 2004. Molecular diagnosis of 55 kinds of single gene diseases can be conducted in clinical practice, including spinal muscular atrophy, fragile X syndrome, mitochondrial encephalomyopathy, Duchenne muscular dystrophy, and spinocerebellar ataxia.<sup>[14,15]</sup> In the mainland of China, just recently medical genetics is emphasized by governmental and educational institutions. The example is the establishment of the Center of Medical Genetics of Peking University in June 2005.<sup>[2]</sup> These institutions aim to train professionals in medical genetics, who will direct the diagnosis and quality control of genetic diseases of children. We hope that the Ministry of Health will help the establishment of genetic departments in the hospitals of key universities throughout the country, promoting the development of diagnosis and prevention of genetic diseases.

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